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An approach for measuring local electric tissue properties in-vivo is proposed. The technique relies upon the integration of MRI data with electrical potential measurements. Through a technique referred to as constrained electric impedance tomography (CEIT), the conductivity of specific regions identified in MRI data can be calculated. A two-dimensional simulation of a phantom containing three-regions of varying electrical conductivity was generated and a finite-element model of electrical current propagation created. The geometry encompassed a total of 24 electrodes arranged around the object with voltages applied between all possible electrode pairs. The resulting potentials for the remaining electrodes were calculated. In order to constrain the reconstruction, co-registered MRI data was used to define the boundaries of the internal structures. Conductivity values were assigned to these regions and the resulting field patterns calculated form a finite element model of the problem. The assumed conductivity was adjusted with an iterative nonlinear optimization technique that minimized the difference between the calculated and measured electrode potentials. When used in the absence of noise, the calculations converged quickly toward the correct conductivity values. However, with the addition of noise (SNR=10), we noted conductivity errors of ~20% for high conductivity structures. These encouraging results demonstrate the electric impedance tomography reconstruction is possible by integrating MRI derived spatial constraints. Further improvement would be expected in a full 3D geometry to provide a greater number of independent measures for the iteration process. Further research in this topic is warranted.

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Constrained MRI Impedance Imaging

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INTRODUCTION

Medical Imaging methods have progressed at an unprecedented pace in the past two decades. With the introduction of Computed Tomography (CT) in the mid 70's, followed by improvements in Ultrasound and the introduction of Magnetic Resonance Imaging in the mid 1980's, medical imaging moved from a medical imaging predominated by projection imaging to a fully 3D imaging discipline. These techniques offer a broad range of approaches for anatomical imaging, but the capability to measure and image biological processes or tissue signatures relevant to diseases features remains a major objective of modern medical imaging research. Several novel imaging signals have been proposed which may offer novel approaches to resolve these challenges. These include the use of optical techniques of fluorescence or Raman scattering, optical coherence tomography, acoustical signatures for biomechanical tissue properties, microwave assessment of internal tissue temperature and functional brain imaging based on magnetic phenomena. In addition, there has been a long standing interest in the exploration of the electrical properties of tissues. Several investigators[1,2] have shown that there are significant changes in both the conductivity and impedance among varying human tissues which could be an alternative mechanism for disease detection. In this study, we explore an alternative method for measuring these properties in-vivo.

ELECTRIC IMPEDANCE TOMOGRAPHY

A number of investigators have explored the concept of measuring tissue bio-impedance properties in-vivo through the use of "Electric Impedance Tomography" (EIT). The technique

involves the use of an array of electrodes distributed around the anatomy of interest[2,3,4]. By applying potentials to these electrodes and measuring the current and potential distribution from one electrode to another, a measure of the tissue properties can be obtained. But considering all possible electrode combinations, it is possible to acquire multiple "views" of the anatomy based on the injected current from multiple directions throughout the anatomy. Unlike CT, the current paths are not rectilinear that would otherwise make them amendable to well know filter back-projection reconstruction methods. Rather, the current paths are characterized by complex curvilinear paths, the geometry of which depends on the very electrical parameters we hope to measure. As such, EIT is classified as an inverse boundary value problem which is ill-posed. Finding stable and efficient solutions to this inverse problem has challenged many talented investigators over the past two decades and still represents an area of intense research[5,6]. In this project, we chose not to attack this problem directly, but to address it in another manner. Our work is based on Magnetic Resonance Imaging (MRI).

MAGNETIC RESONANCE IMAGING

Our group has been involved in the development of MRI techniques for a number of years. One of the main applications which we have been exploring is the role of MRI in the detection of breast cancer and in particular its role in the screening of women at elevated risk arising from mutations to the breast cancer genes BRCA1/BRCA2 [7]. Our studies have shown that breast MRI offers significant advantage over other breast imaging modalities for the detection of breast cancer in younger women, who present with dense breasts and for whom breast cancer prognosis is often poor. In the course of our work, we have shown that the sensitivity of breast MRI is approximately two fold more sensitive than any other single modality including mammography, ultrasound or clinical examination. Specifically, we have shown from data gathered over a five period, that the sensitivity of breast MRI showed a sensitivity of 82% compared to 32% for mammography, 36% for ultrasound and 11% for clinical examination. This finding is particularly important as MRI exhibits high sensitivity in this special, high-risk group, in whom high breast density is frequently present; a feature which

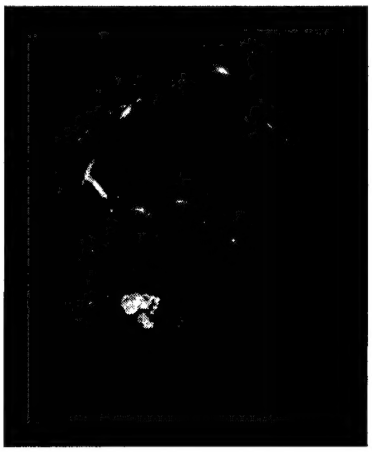

Figure 1. Contrast enhanced breast MRI of a tumour in a high risk patient

often limits imaging by mammography. A typical example of a breast MRI is shown in Figure 1, which illustrates the fine detail and excellent soft tissue contrast of an enhancing tumour mass. Our work[8], together with finding from other studies[9,10,11] suggests that MRI will play a critical role in breast imaging of this population in the near future.

While the sensitivity of breast MRI is high, the specificity remains less than ideal. As some kinds of normal tissue (lymph nodes), benign processes (fibroadenomas) as well as malignant tumours can show signal increases under Gd-DTPA enhanced MRI, the clear distinction of these different tissue types remains challenging. Various approaches to address this problem are based on the use of kinetics of assessment and lesion morphology. Several studies have shown that specificity can vary significantly depending on the patient population and the approach used. Drawn from the work of a number of investigators, the specificity of MRI has been reported with values ranging from 37%-97% [12]. During the last five years of screening we have experienced a sensitivity of 82%. However, a feature of greater interest, is the positive predictive value (PPV), that reflects the frequency with which MRI detected lesions sent to biopsy prove to be malignant. In our own experience, we found a PPV of 37% from data drawn throughout the five years of our study. Obviously, MRI is a sensitive technique, but its specificity could be improved. It is this feature, which has motivated us to explore other areas to improve our ability to classify regions of enhancement.

CONSTRAINED MAGNETIC RESONANCE ELASTOGRAPHY (C-MRE)

During the past several years, our group has been exploring other means to augment the power of MRI to diagnose breast lesions by coupling the exquisite soft tissue capabilities and high resolution of MRI with other probes to interrogate tissues. One example is through Elastography[13]. In this approach, we mechanically stimulate tissues while measuring the spatial distribution of motions with phase contrast MRI. The resulting motions are determined by the distribution of viscoelastic properties through the tissues of interest. Through knowledge of the physics of how these viscoelastic forces propagate through tissue, we can estimate the nature of the tissue properties by creating images of the elastic properties of tissues. In many ways, the problem of MRE is similar to that of EIT in that the factors which influence each point in the MRE

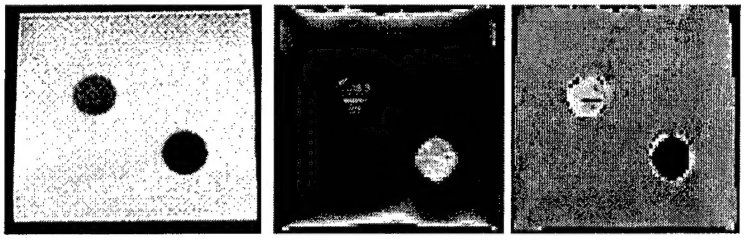

Figure 2. MRI image of a phantom with a soft background containing two harder lesions(left), the strain image of the phantom (middle), the constrained reconstruction of the distribution of modulus (right).

images are influenced by the properties surrounding that point. The net result is that some form of inverse solution is needed. We have explored the area of Quasi-Static MRE and shown that generalized inverse solutions to this problem are very demanding in terms of the imaging signal/noise in order to reconstruct the elastic properties reliably. As an alternative, we have introduced the concept of a constrained Elastography reconstruction[13]. In this concept, we recognize that through conventional contrast-enhanced MRI, we have a-priori knowledge of the presence of a tumour and the exact three dimensional spatial locations of the suspicious region and surrounding breast tissue. We use this information for help solve the inverse solution. The net result is that rather than having images with 256x256 pixels of unknown elastic modulus, we assume that the suspicious region has a uniform modulus while the background tissues have other values. The spatial requirements for the problem drop out and we are left with a problem with only a few unknowns; namely, the modulus of the tumour and those of surrounding normal tissue regions. We have shown that by making this assumption, there can be substantial reductions in the signal/noise requirements while maintaining the spatial resolution of the MRI data[14]. An example taken from this work is shown in Figure 2 which shows a breast phantom containing a pair of lesions of known modulus which were 2 and 5 times greater modulus than the background. The MRI image shows the lesions clearly, while the strain data also indicates the location of the lesion. The calculated modulus data (right) shows the variation of the modulus which is in excellent agreement with the known lesion modulus. We conclude that through constrained reconstruction we can effectively reach inverse solutions with much reduced SNR requirement when there is a-priori information is applied. It was this experience that leads us to consider a similar solution to other inverse problems such as the question of imaging the electrical impedance of tissues.

CONSTRAINED ELECTRICAL IMPEDANCE TOMOGRAPHY (CEIT)

Rather than probing for biomechanical properties, we aim to measure the electrical properties of tissue. Previous studies[2,2] have shown that variations in tissue electrical conductivity appear to be correlated to the presence of neoplasia and thereby may represent an interesting signal for improved specificity. Again, we assume that we have information about the exact shape of the object (the breast), the position of fat and fibroglandular tissues as well as any suspicious masses with which we may be concerned. We use this information in creating a model of the breast which we can use to test for its electrical properties. By making assumptions of

uniformity of electrical conductivity of the normal and abnormal tissues throughout their respective regions, we then simulate the effects of varying electrode geometries. Our remaining task is to adjust the conductivity of each region until we reach agreement with our measured data. Once this has been achieved, we then assign the corresponding conductivity values to each tissue of interest.

It should be noted that a number of key assumptions are made in carrying out this work. First, we assume that the region of concern throughout the tissue as seen by contrast-enhanced MRI will also exhibit a variation in electrical conductivity. Second, we assume that the normal regions will have uniform electrical properties throughout. Third, we assume that only the materials which can be seen by the MRI scans will effect the electrical properties and that there will be no other material in the object which might influence the conductivity of the object. Finally, we assume that the lesion will have a uniform electrical property throughout its volume. Thus, we can see that many assumptions need to be met in order to adequately interpret the CEIT data; however, given its prospective use, this may indeed provide new and useful information for breast MRI data which could be unique.

RESEARCH TASKS

This project was aimed at providing basic theoretical evidence that CEIT would be practical and of advantage over EIT. Specifically, we proposed to develop an appropriate reconstruction framework to assess the properties of CEIT and explore its properties in numerical simulations. Our main goal was to determine the noise properties of the system and its potential accuracy in simple phantom geometries.

METHODS:

The study involved creating a model problem with an appropriate distribution of electrodes and voltage measurements. The object we chose is shown in Figure 3 and is composed of a structure with three regions with conductivities of 1, 5 and 25 S/m. While the number of electrodes which can be

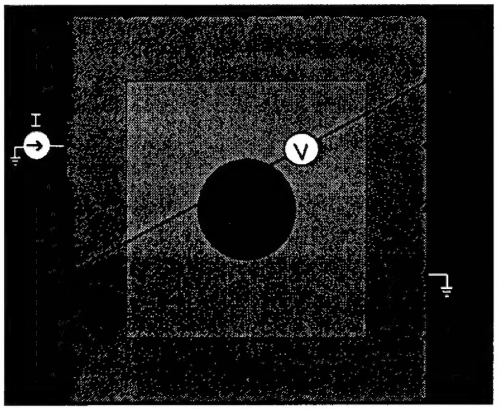

Figure 3. A potential measurement across a pair of electrodes for a given geometry of applied voltage.

placed around the object is arbitrary, we chose to consider only 24 electrodes for this exploratory work. Each electrode is distinguished as a tiny black mark on the periphery of the object. We then created a mesh for the finite element modeling. The relation between the potential and electric current is modeled in the form of a variational integral boundary value problem which solves the following equation :

$$\int_v \nabla \delta\Phi \cdot \sigma \cdot \nabla \Phi dV = \int_s \delta\Phi J dS$$

where $\nabla\delta\Phi$ is the electrical field potential, σ is the tissue conductivity, and J is the current density which is calculated over a surface S [15]. The surface potential is calculated for a given set of boundary conditions by finite element methods. A typical current distribution for a calculation when the potential is uniform across the top of the phantom is shown in Figure 4. Here we can see the central inclusion clearly as a region of higher current density passing through this region compared to the surrounding regions of lower conductivity. The essence of the constrained reconstruction is to create a model of the object for forward calculations of the electric fields and compare results derived from this model field to those derived experimentally. For example, the current injection and the potential measurements could be made as shown in Figure 3. Given that there are a number of potential current injection grounding and measurement points, a large number of measurements can be made. To solve for the unknown conductivities, we use a non-linear optimization algorithm to estimate the conductivities in a series of steps, whereby the values for the three regions are adjusted iteratively until the difference between the predicted potentials and those seen experimentally is minimized. This algorithm makes the assumption that the conductivity is isotropic and uniform within a specified region. In this case, three unknown values of conductivity are to be determined, while the spatial extent of these regions is to be inferred from the MRI data. The question that remains is

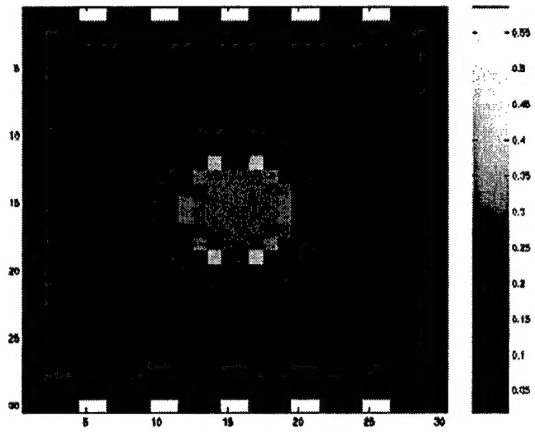

Figure 4.Calculated current for the phantom with a uniform potential across the top array of electrodes .

the stability of the estimation, its accuracy and the sensitivity to noise in the measurement data itself.

RESULTS

In order to test this concept, we explored the stability of the reconstruction in the presence of varying amounts of noise. In the absence of measurement noise, we have found that it is possible to reconstruct the values of the three regions with high accuracy. The reconstructions are stable and iterative process converges rapidly. However, in the presence of measurement noise, we begin to see the effects on the final values for each region. To explore this effect, we calculated the effect of adding noise to the measurement values that were 1%, 5% and 10% of the potential at the voltage injection site throughout all the measurement points. This data is shown in Table I. With small noise levels, it is clear that the accuracy is good but we note that it begins to degrade with increased noise levels approaching 10%. The noise value, as applied, represents a measure of the noise level introduced on each measurement as a fraction of the applied potential. While a useful first approximation of noise, this tends to overestimate the relevant noise in the detected signals. These data show that the accuracy of the reconstructed conductivity as better maintained for the high conductivity structures as noise was added compared to the background which experienced larger variations. This is likely due to the fact that with increased conductivity, more current from varying electrodes would pass through the lesions compared to the more uniform background. These simulations indicate that reconstructions can indeed be performed in a stable manner as seen by the limited number of interactions needed to reach a convergent value.

Table 1. Estimated conductivity for the three regions (C1, C2, and C3), the residual of the optimization problem and number of iterations required for convergence as a function of source noise levels. The ideal values of C1,C2 and C3 are 1,5 and:25 S/m respectively.

Noise	Residual	C1 (S/m)	C2 (S/m)	C3 (S/m)	Iteration #
1%	1.23	0.99	5.0	24.48	8
5%	34.8	0.82	4.02	24.33	20
10%	140.6	0.56	6.75	20.81	15

It should be noted that these simulations where done in two dimensions. The next step is to extend these calculations to a three dimensional model. We believe that this will improve the operation of this technique in that the number of unique degrees of freedom which can be exploited in estimating the conductivity will increase. For example, if we surround a 2D structure with N measurement points, then in principle we apply N^2 measurements in a 3D model. The net result will be that we will increase the number of independent measurements of the object that will operate to drive the reconstruction to a unique solution. While some progress was made in starting this work, we cannot report substantial findings at this time. However, we do feel that this represents a fruitful area for further investigation in the form of numerical simulations which may lead ultimately toward an experimental system.

KEY RESEARCH ACCOMPLISHMENTS

We have devised a novel method for conducting measurement of electrical conductivity within specified regions of tissues derived form medical imaging data. The specific accomplishments to date are:

1) The development of a 2D finite element model of electric fields and currents in arbitrary structures,

2) Software development of the iterative constrained reconstruction process for electrical impedance measurements

3) Exploration of a number of iterations needed to provide converge to a stable solution.

4) Study of the accuracy of the reconstructed tissue conductivity under different noise levels.

5) We have demonstrated that CEIT offers significant advantages over conventional EIT in application to geometries such as the breast. We are encouraged by these data

which suggest that this concept is worthy of further research.

REPORTABLE OUTCOMES

The specific outcomes of this work are based on the studies outlined above through numerical simulations and the development of a specific methodology for constrained reconstruction as applied to EIT. We have explored the topic to a degree that gives us confidence that it warrants further investigation. These will be the subject of future reports, papers and abstracts when augmented by future studies.

In addition, one of the key participants in this research who conducted most of the studies was Dr. A Samani who worked with me as a research associate. Dr. Samani has extensive experience in the area of inverse problems and finite element analysis. This project was one of those to which he devoted considerable effort. Since that time, Dr. Samani has since secured a research/teaching faculty position at the University of Western Ontario in the area of medical imaging, biomechanics and inverse problems. During his recruitment his experience in constrained reconstruction methods was one of the areas he highlighted as his areas of expertise and future research objectives which lead to his recruitment. As such, his work in this area was a key factor in his successful recruitment and a pivotal step in moving his research career forward. Dr. Samani will be carrying on work in the area of constrained reconstruction in the future.

In addition, we supported two undergraduate coop students with this project funding. The first student was hired during the summer of 2002 and was from electrical engineering who developed the finite element solver for the problem and developed the initial non-linear iterative solution for the method. A second student was hired in the fall of 2003 who conducted the development of numerical phantom and noise analysis. As such, a total of three individuals were supported in part through this funding.

CONCLUSIONS:

In this proposal, which was conducted over the course of ~1.5 years, we have shown that it is possible to apply a constrained approach to the estimation of electrical conductivity within structures similar to the dimensions of breast anatomy. Our findings support the general

hypothesis that constrained inverse methods for impedance imaging are feasible and strongly believe this concept warrants further investigation. The potential for integrating CEIT with MRI breast imaging represents a unique and novel approach, which to the best of our knowledge, has not been proposed before. The potential to elucidate new information that will aid in the appreciation of masses detected in contrast enhanced breast MRI is significant. This represents an example of how constrained integration of 3D imaging data with other imaging or biological probes can be used. It represents a general approach that will allow the integration of a wider array of potentially interesting biological signals, of which electrical conductivity is but one example. When applied in conjunction with MRI or any other 3D or tomographic imaging system, this may to allow a measure of electrical properties of suspicious tissue regions. A number of key assumptions need to be recognized in order to interpret this data and as a result the applicability of the concept to clinical problems needs to be addressed in their proper context. For example, constrained reconstruction tells us nothing regarding the spatial distribution of disease but it does give us a model with which to probe the electrical properties of known structures. Thus, CEIT might best be described as a measurement method rather than an imaging system. Nevertheless, this concept could be of value to augment our understanding of breast tissues which may serve as surrogate signature to aid in differentiating tissue types. We will continue to explore this concept under separate and future studies.

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